Skin Notation (SK) Profile

Dioxathion

[CAS No. 78-34-2]

Department of Health and Human Services
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health

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Suggested Citation

NIOSH [20XX]. NIOSH skin notation profile:Dioxathion. By Hudson NL, Dotson GS. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. XXX

DHHS (NIOSH) Publication No. XXX

Foreword

As the largest organ of the body, the skin performs multiple critical functions, such as serving as the primary barrier to the external environment. For this reason, the skin is often exposed to potentially hazardous agents, including chemicals, which may contribute to the onset of a spectrum of adverse health effects ranging from localized damage (e.g., irritant contact dermatitis and corrosion) to induction of immune-mediated responses (e.g., allergic contact dermatitis and pulmonary responses), or systemic toxicity (e.g., neurotoxicity and hepatoxicity). Understanding the hazards related to skin contact with chemicals is a critical component of modern occupational safety and health programs.

In 2009, the National Institute for Occupational Safety and Health (NIOSH) published *Current Intelligence Bulletin (CIB) 61 – A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009-147]. This document provides the scientific rationale and framework for the assignment of multiple hazard-specific skin notations (SK) that clearly distinguish between the systemic effects, direct (localized) effects, and immune-mediated responses caused by skin contact with chemicals. The key step within assignment of the hazard-specific SK is the determination of the hazard potential of the substance, or its potential for causing adverse health effects as a result of skin exposure. This determination entails a health hazard identification process that involves use of the following:

- Scientific data on the physicochemical properties of a chemical
- Data on human exposures and health effects
- Empirical data from *in vivo* and *in vitro* laboratory testing
- Computational techniques, including predictive algorithms and mathematical models that describe a selected process (e.g., skin permeation) by means of analytical or numerical methods.

This *Skin Notation Profile* provides the SK assignments and supportive data for dioxathion. In particular, this document evaluates and summarizes the literature describing the hazard potential of the substance and its assessment according to the scientific rationale and framework outlined in CIB 61. In meeting this objective, this *Skin Notation Profile* intends to inform the audience—mostly occupational health practitioners, researchers, policy- and decision-makers, employers, and workers in potentially hazardous workplaces—so that improved risk-management practices may be developed to better protect workers from the risks of skin contact with the chemicals of interest.

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Contents

Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
CIB	Current Intelligence Bulletin
cm^2	squared centimeter(s)
cm/hr	centimeter(s) per hour
cm/s	centimeter(s) per second
DEREK	Deductive Estimation of Risk from Existing Knowledge
DIR	skin notation indicating the potential for direct effects to the skin following contact with a chemical
EC	European Commission
g	gram(s)
g/L	gram(s)/liter
GHS	Globally Harmonized System for Classification and Labelling of Chemicals
GPMT	guinea pig maximization test
hr	hour(s)
IARC	International Agency for Research on Cancer
IPCS	International Program for Chemical Safety
(IRR)	subnotation of SK: DIR indicating the potential for a chemical to be a skin irritant following exposure to the skin
k_{aq}	coefficient in the watery epidermal layer
k_p	skin permeation coefficient
k_{pol}	coefficient in the protein fraction of the stratum corneum
k_{psc}	permeation coefficient in the lipid fraction of the stratum corneum
LD_{50}	dose resulting in 50% mortality in the exposed population
LD_{Lo}	dermal lethal dose
LLNA	local lymph node assay
LOAEL	lowest-observed-adverse-effect level
log K_{OW}	base-10 logarithm of a substance's octanol–water partition
M	molarity
m^3	cubic meter(s)
mg	milligram(s)
$mg/cm^2/hr$	milligram(s) per square centimeter per hour
mg/kg	milligram(s) per kilogram body weight
mg/m^3	milligram(s) per cubic meter
mL	milliliter(s)
mL/kg	milliliter(s) per kilogram body weight
MW	molecular weight
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program

OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
ppm	parts per million
REL	recommended exposure limit
RF	retention factor
SEN	skin notation indicating the potential for immune-mediated reactions following exposure of the skin
SI ratio	ratio of skin dose to inhalation dose
SK	skin notation
S_W	solubility in water
SYS	skin notation indicating the potential for systemic toxicity following exposure of the skin
USEPA	United States Environmental Protection Agency
µg	microgram(s)
µg/cm^2	microgram(s) per square centimeter
µg/cm^2/hr	microgram(s) per square centimeter per hour
µL	microliter(s)
µmol	micromole(s)

Glossary

Absorption—The transport of a chemical from the outer surface of the skin into both the skin and systemic circulation (including penetration, permeation, and resorption).

Acute exposure—Contact with a chemical that occurs once or for only a short period of time.

Cancer—Any one of a group of diseases that occurs when cells in the body become abnormal and grow or multiply out of control.

Contaminant—A chemical that is (1) unintentionally present within a neat substance or mixture at a concentration less than 1.0% or (2) recognized as a potential carcinogen and present within a neat substance or mixture at a concentration less than 0.1%.

Cutaneous (or percutaneous)—Referring to the skin (or through the skin).

Dermal—Referring to the skin.

Dermal contact—Contact with (touching) the skin.

Direct effects—Localized, non-immune-mediated adverse health effects on the skin, including corrosion, primary irritation, changes in skin pigmentation, and reduction/disruption of the skin barrier integrity, occurring at or near the point of contact with chemicals.

Immune-mediated responses—Responses mediated by the immune system, including allergic responses.

Sensitization—A specific immune-mediated response that develops following exposure to a chemical, which, upon re-exposure, can lead to allergic contact dermatitis (ACD) or other immune-mediated diseases such as asthma, depending on the site and route of re-exposure.
Substance—A chemical.

Systemic effects—Systemic toxicity associated with skin absorption of chemicals after exposure of the skin.

Acknowledgments

This document was developed by the Education and Information Division (Paul Schulte, Ph.D., Director). G. Scott Dotson, Ph.D., was the project officer for this document, assisted in great part by Naomi Hudson, Dr.P.H., MPH, Paul Siegel, Ph.D. and Todd Niemeier, M.Sc. The basis for this document was a report (*Toxicology Excellence for Risk Assessment [TERA]*) contracted by NIOSH and prepared by Bernard Gadagbui, Ph.D., and Andrew Maier, Ph.D.

For their contribution to the technical content and review of this document, special acknowledgment is given to the following NIOSH personnel:

Denver Field Office
Eric Esswein, M.Sc.

Division of Applied Research and Technology
Clayton B'Hymer, Ph.D.
John Snawder, Ph.D.

Division of Respiratory Disease Studies
Gregory A. Day, Ph.D.
Aleksander Stefaniak, Ph.D.

Division of Surveillance, Hazard Evaluations, and Field Studies
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Aaron Sussell, Ph.D.
Loren Tapp, M.D.

Education and Information Division
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Thomas J. Lentz, Ph.D.
Richard Niemeier, Ph.D.
Ralph Zumwalde, M.Sc.

Health Effects Laboratory Division
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H. Fredrick Frasch, Ph.D.
Michael Luster, Ph.D.
Anna Shvedova, Ph.D.
Paul Siegel, Ph.D.
Berran Yucesoy, Ph.D.

National Personal Protective Technology Laboratory
Heinz Ahlers, J.D., M.Sc.
Angie Shepherd

For their contribution to the technical content and review of this document, special acknowledgment is given to the following CDC personnel:

Office of Surveillance, Epidemiology and Laboratory Services/Epidemiology and Analysis Program Office
Barbara Landreth, M.A.

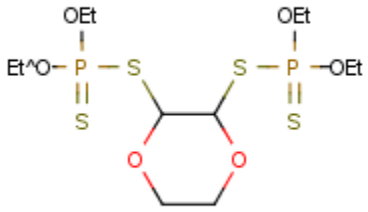
In addition, special appreciation is expressed to the following individuals for serving as independent, external reviewers and providing comments that contributed to the development or improvement of this document:

- G. Frank Gerberick, Ph.D., The Procter and Gamble Company, Cincinnati, OH
- Dori Germolec, Ph.D., National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle, NC
- Ben Hayes, M.D., Ph.D., Division of Dermatology, Vanderbilt School of Medicine, Nashville, TN
- Jennifer Sahmel, M.Sc., CIH, ChemRisk, Boulder, CO
- James Taylor, M.D., Industrial Dermatology, The Cleveland Clinic, Cleveland, OH

1.0 Introduction

1.1 General Substance Information:

Chemical: Dioxathion
CAS No: 78-34-2
Molecular weight (*MW*): 456.6
Molecular formula: $C_4H_6O_2[SPS(OC_2H_5)_2]_2$
Structural formula:



Synonyms: Delnav®, p-Dioxane-2,3-diyl ethyl phosphorodithioate, Dioxane phosphate, 2,3-p-Dioxanethiol-S,S-bis(O,O-diethyl phosphorodithioate), Navadel

Uses: Dioxathion is an organophosphate pesticide [HSDB 2009]. No data were identified to determine the volume of the pesticide currently or historically produced in the United States.

1.2 Purpose

This skin notation profile presents (1) a brief summary of epidemiological and toxicological data associated with skin contact with dioxathion and (2) the rationale behind the hazard-specific skin notation (SK) assignment for dioxathion. The SK assignment is based on the scientific rationale and logic outlined in the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009]. The summarized information and health hazard assessment are limited to an evaluation of the potential health effects of dermal exposure to dioxathion. A literature search was conducted through February 2013 to identify information on dioxathion, including but not limited to data relating to its toxicokinetics, acute toxicity, repeated-dose systemic toxicity, carcinogenicity, biological system/function–specific effects (including reproductive and developmental effects and immunotoxicity), irritation, and sensitization. Information was considered from studies of humans, animals, or appropriate modeling systems that are relevant to assessing the effects of dermal exposure to dioxathion.

1.3 Overview of SK Assignment

Dioxathion is potentially capable of causing numerous adverse health effects following skin contact. A critical review of available data has resulted in the following SK assignment for dioxathion: **SK: SYS (FATAL)**. Table 1 provides an overview of the critical effects and data used to develop the SK assignment for dioxathion.

Table 1. Summary of the SK Assignment for dioxathion

Skin Notation	Critical Effect	Available Data
SK: SYS (FATAL)	Acute toxicity; Acutely fatal	Sufficient animal data

2.0 Systemic Toxicity from Skin Exposure (SK: SYS)

No toxicokinetic studies were identified in humans or in animals that estimated the degree of absorption of dioxathion through the skin following dermal exposure. The potential of dioxathion to pose a skin absorption hazard was evaluated, with use of a predictive algorithm for estimating and evaluating the health hazards of dermal exposure to substances [NIOSH 2009]. The evaluation method compares an estimated dose accumulated in the body from skin absorption and an estimated dose from respiratory absorption associated with a reference occupational exposure limit. On the basis of this algorithm, a ratio of the skin dose to the inhalation dose (SI ratio) of 0.0027 was calculated for dioxathion. An SI ratio of ≥0.1 indicates that a chemical is capable of producing systemic toxicity from skin exposure [NIOSH 2009]; therefore, dioxathion is not considered to be absorbed through the skin following dermal exposure. Additional information on the SI ratio and the variables used in its calculation are included in the appendix.

No estimates of the dermal lethal dose (LD_{Lo}) of dioxathion for humans were identified. However, acute dermal LD_{50} values (the dose resulting in 50% mortality in the exposed animals) of 63 and 235 milligrams per kilogram body weight (mg/kg) were reported in female and male rats, respectively, when dioxathion was applied in xylene [Gaines 1969]. The dermal LD_{50} value for m-xylene, for which data were available, is 14.1 millilitres per kilogram body weight (mL/kg, corresponding to 12,126 mg/kg) in rabbits [Smyth et al. 1960], indicating that the observed value for dioxathion was not due to xylene toxicity. In rabbits, dermal LD_{50} values for a commercial preparation of dioxathion containing 70% *cis* and *trans* isomers (present in the ratio of 1:2, respectively) were reported as 106 mg/kg in the absence of a solvent and 100 mg/kg applied in xylene as a solvent in rabbits and 63 and 235 mg/kg of the commercial preparation of dioxathion applied in xylene in female and male rats, respectively [Frawley et al. 1963]. Because the reported acute dermal LD_{50} values for female rats and for rabbits are lower than the critical cutoff dermal LD_{50} value of 200 mg/kg body weight that identifies chemical substances with the potential to be fatal at low doses [NIOSH 2009], dioxathion is considered acutely fatal following dermal exposure.

No case reports or epidemiological studies or animal repeated dose, subchronic or chronic toxicity studies were identified that evaluated the potential of dioxathion to cause systemic effects following

dermal exposure. No specialty studies were identified that evaluated the potential of dioxathion to cause biological system/function specific effects (including reproductive and developmental effects and immunotoxicity) following dermal exposure. No epidemiological studies or animal bioassays were identified that evaluated the potential of dioxathion to be carcinogenic or co-carcinogenic following dermal exposure. However, agencies or organizations have evaluated the carcinogenic potential of dioxathion following other routes of exposure. Table 2 summarizes carcinogenic designations of multiple governmental and nongovernmental organizations for dioxathion.

Table 2. Summary of the carcinogenic designations for dioxathion by numerous governmental and nongovernmental organizations

Organization	Carcinogenic designation
NIOSH [2005]	No designation
NTP [2014]	No designation
USEPA [2015]	No designation
European Parliament [2008]	No GHS designation
IARC [2012]	No designation
EC [2013]*	No designation
ACGIH [2002]	A4: Not classifiable as a human carcinogen

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; GHS = Globally Harmonized System for Classification and Labelling of Chemicals; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; USEPA = United States Environmental Protection Agency.
*Date accessed.

No toxicokinetic data in humans or animals were identified that evaluated the potential of dioxathion to be absorbed through the skin following dermal exposure. Although a predictive model indicates that dioxathion has low potential to be absorbed through the skin and be systemically available, acute dermal toxicity studies in rats and rabbits **[Frawley et al. 1963; Gaines 1969]**[1] indicate dioxathion is absorbed through the skin, is systemically available, and can be fatal at low doses. Therefore, on the basis of the data for this assessment, dioxathion is assigned the SK: SYS (FATAL) notation.

3.0 Direct Effects on Skin (SK: DIR)

No human or animal *in vivo* studies that evaluated the corrosivity of dioxathion or *in vitro* tests for corrosivity using human or animal skin models or *in vitro* tests of skin integrity using cadaver skin were identified. No case reports or clinical studies or standard skin irritation tests were identified that evaluated the potential of dioxathion to cause skin irritation. The lack of *in vitro* tests, case reports or standard skin irritation tests precludes adequate evaluation of the potential of dioxathion to produce direct effects on the skin. Therefore, on the basis of the data for this assessment, dioxathion is not assigned the SK: DIR (IRR) notation.

[1]References in **bold** text indicate studies that serve as the basis of the SK assignments.

4.0 Immune-mediated Responses (SK: SEN)

Studies that evaluated skin sensitization following dermal exposure to dioxathion were not identified. No reports of sensitization in humans or predictive tests (for example, guinea pig maximization tests, Buehler tests, murine local lymph node assays, mouse ear swelling tests) or other tests that evaluated the potential of dioxathion to cause skin sensitization in animals were identified. The lack of diagnostic tests in humans and predictive tests in animals precludes adequate evaluation of the potential of dioxathion to cause skin sensitization. Therefore, on the basis of the data for this assessment, dioxathion is not assigned the SK: SEN notation.

5.0 Summary

No toxicokinetic data in humans or animals, or case reports, epidemiological studies or repeated dose, subchronic or chronic toxicity studies in animals were identified that evaluated the potential of dioxathion to be absorbed through the skin or to cause systemic effects following dermal exposure. Although a predictive model indicates that dioxathion has low potential to be absorbed through the skin and be systemically available, acute dermal toxicity studies in rats and rabbits **[Frawley et al. 1963; Gaines 1969]** indicate that dioxathion is absorbed through the skin, is systemically available, and can be fatal at low doses following dermal exposure. No *in vitro* tests, case reports or standard skin irritation tests were identified that evaluated the potential of dioxathion to produce direct effects on the skin. No diagnostic tests in humans or predictive tests in animals were identified to adequately evaluate the potential of dioxathion to cause skin sensitization. Therefore, on the basis of these assessments, dioxathion is assigned a composite skin notation of **SK: SYS (FATAL)**.

Table 3 summarizes the skin hazard designations for dioxathion previously issued by NIOSH and other organizations. The equivalent dermal designations for dioxathion, according to the Global Harmonization System (GHS) of Classification and Labelling of Chemicals, is Acute Toxicity Category 3 (Hazard statement: Toxic in contact with the skin) [European Parliament 2008].

Table 3. Summary of previous skin hazard designations for dioxathion

Organization	Skin hazard designation
NIOSH [2005]	[skin]: Potential for dermal absorption; prevent skin contact
OSHA [2015]*	No designation
ACGIH [2002]	[skin]: Based on severe symptoms of organophosphate poisoning produced in animals following relatively small dermal doses
EC [2013]*	R21: Toxic in contact with skin

ACGIH = American Conference of Governmental Industrial Hygienists; EC = European Commission, Joint Research, Institute for Health and Consumer Protection; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration.
*Date accessed.

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Appendix: Calculation of the SI Ratio for Dioxathion

This appendix presents an overview of the SI ratio and a summary of the calculation of the SI ratio for dioxathion. Although the SI ratio is considered in the determination of a substance's hazard potential following skin contact, it is intended only to serve as supportive data during the assignment of the NIOSH SK. An in-depth discussion on the rationale and calculation of the SI ratio can be found in Appendix B of the *Current Intelligence Bulletin (CIB) 61: A Strategy for Assigning New NIOSH Skin Notations* [NIOSH 2009].

Overview

The SI ratio is a predictive algorithm for estimating and evaluating the health hazards of skin exposure to substances. The algorithm is designed to evaluate the potential for a substance to penetrate the skin and induce systemic toxicity [NIOSH 2009]. The goals for incorporating this algorithm into the proposed strategy for assigning SYS notation are as follows:

(1) Provide an alternative method to evaluate substances for which no clinical reports or animal toxicity studies exist or for which empirical data are insufficient to determine systemic effects.
(2) Use the algorithm evaluation results to determine whether a substance poses a skin absorption hazard and should be labeled with the SYS notation.

The algorithm evaluation includes three steps:
(1) determining a skin permeation coefficient (k_p) for the substance of interest,
(2) estimating substance uptake by the skin and respiratory absorption routes, and
(3) evaluating whether the substance poses a skin exposure hazard.

The algorithm is flexible in the data requirement and can operate entirely on the basis of the physicochemical properties of a substance and the relevant exposure parameters. Thus, the algorithm is independent of the need for biologic data. Alternatively, it can function with both the physicochemical properties and the experimentally determined permeation coefficient when such data are available and appropriate for use.

The first step in the evaluation is to determine the k_p for the substance to describe the transdermal penetration rate of the substance [NIOSH 2009]. The k_p, which represents the overall diffusion of the substance through the stratum corneum and into the blood capillaries of the dermis, is estimated from the compound's molecular weight (*MW*) and base-10 logarithm of its octanol–water partition coefficient ($\log K_{ow}$). In this example, k_p is determined for a substance with use of Equation 1. A self-consistent set of units must be used, such as centimeters per hour (cm/hr), outlined in Table A1. Other model-based estimates of k_p may also be used [NIOSH 2009].

Equation 1: Calculation of Skin Permeation Coefficient (k_p)

$$k_p = \frac{1}{\frac{1}{k_{psc} + k_{pol}} + \frac{1}{k_{aq}}}$$

where k_{psc} is the permeation coefficient in the lipid fraction of the stratum corneum, k_{pol} is the coefficient in the protein fraction of the stratum corneum, and k_{aq} is the coefficient in the watery epidermal layer. These components are individually estimated by

$\log k_{psc} = -1.326 + 0.6097 \times \log K_{ow} - 0.1786 \times MW^{0.5}$
$k_{pol} = 0.0001519 \times MW^{-0.5}$
$k_{aq} = 2.5 \times MW^{-0.5}$

The second step is to calculate the biologic mass uptake of the substance from skin absorption (skin dose) and inhalation (inhalation dose) during the same period of exposure. The skin dose is calculated as a mathematical product of the k_p, the water solubility (S_w) of the substance, the exposed skin surface area, and the duration of exposure. Its units are milligrams (mg). Assume that the skin exposure continues for 8 hours to unprotected skin on the palms of both hands (a surface area of 360 squared centimeters [cm^2]).

Equation 2: Determination of Skin Dose

Skin dose = $k_p \times S_w \times$ Exposed skin surface area × Exposure time
= k_p(cm/hr) × S_w (mg/cm^3) × 360 cm^2 × 8 hr

The inhalation dose (in mg) is derived on the basis of the occupational exposure limit (OEL) of the substance—if the OEL is developed to prevent the occurrence of systemic effects rather than sensory/irritant effects or direct effects on the respiratory tract. Assume a continuous exposure of 8 hours, an inhalation volume of 10 cubic meters (m^3) inhaled air in 8 hours, and a factor of 75% for retention of the airborne substance in the lungs during respiration (retention factor, or RF).

Equation 3: Determination of Inhalation Dose

Inhalation dose = OEL × Inhalation volume × RF
= OEL (mg/m^3) × 10 m^3 × 0.75

The final step is to compare the calculated skin and inhalation doses and to present the result as a ratio of skin dose to inhalation dose (the SI ratio). This ratio quantitatively indicates (1) the significance of dermal absorption as a route of occupational exposure to the substance and (2) the contribution of dermal uptake to systemic toxicity. If a substance has an SI ratio greater than or equal to 0.1, it is considered a skin absorption hazard.

Calculation

Table A1 summarizes the data applied in the previously described equations to determine the SI ratio for dioxathion. The calculated SI ratio was 0.0027. On the basis of these results, dioxathion is not predicted to represent a skin absorption hazard.

Table A1. Summary of Data used to Calculate the SI Ratio for Dioxathion

Variables Used in Calculation	Units	Value
Skin permeation coefficient		
Permeation coefficient of stratum corneum lipid path(k_{psc})	cm/hr	0.00092
Permeation coefficient of the protein fraction of the stratum corneum (k_{pol})	cm/hr	7.1092×10^{-6}
Permeation coefficient of the watery epidermal layer (k_{aq})	cm/hr	0.117
Molecular weight (MW)*	amu	456.54
Base-10 logarithm of its octanol–water partition coefficient (Log K_{ow})*	None	3.45
Calculated skin permeation coefficient (k_p)	cm/hr	0.0009
Skin dose		
Water solubility (S_w)*	mg/cm^3	0.00155
Calculated skin permeation coefficient (k_p)	cm/hr	0.0009
Estimated skin surface area (palms of hand)	cm^2	360
Exposure time	hr	8
Calculated skin dose	mg	0.00408
Inhalation Dose		
Occupational exposure limit (OEL)†	mg/m^3	0.2
Inhalation volume	m^3	10
Retention factor (RF)	None	0.75
Inhalation dose	mg	1.5
Skin dose–to–inhalation dose (SI) ratio	None	0.0027

*Variables identified from SRC [ND].

†The OEL used in calculation of the SI ratio for dioxathion was the NIOSH recommended exposure limit (REL) [NIOSH 2005].

Appendix References

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